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WHO NEEDS FURTHER ATTENTION?
Assessment of liver disease severity and indications for referral

Dr Tan Soek Siam
Senior Consultant Hepatologist
Selayang Hospital

WHO NEEDS FURTHER ATTENTION?
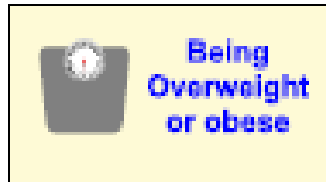
WHY NOT EVERYONE??

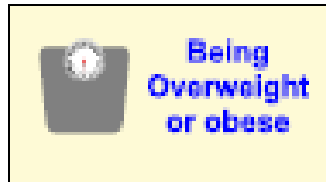Assessment of liver disease severity and indications for referral

Checking for "People who are at risk" of MAFLD in Malaysian NHMS 2019

Risks for MAFLD

Being Overweight or obese

19 Overweight/obesity & abdominal obesity:
A tag team of health risk

1 in 2 adults in Malaysia were overweight or obese

1 in 2 adults in Malaysia had abdominal obesity

M Eslam et al. Hepatology International 2020, NHMS 2019 Institute for Public Health, Malaysia

Checking for "People who are at risk" of MAFLD in Malaysian NHMS 2019

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1 in 2 adults in Malaysia were **overweight or obese**

1 in 2 adults in Malaysia had **abdominal obesity**

04 Diabetes in Malaysia

1 in 5 adults in Malaysia have **diabetes**

That's about **3.9 million** people aged 18 years and above

Increasing trend

M Eslam et al. Hepatology International 2020, NHMS 2019 Institute for Public Health, Malaysia
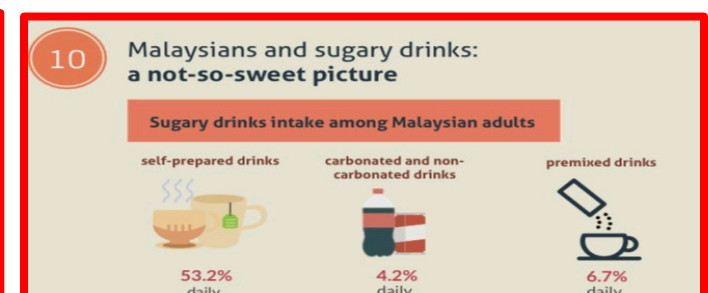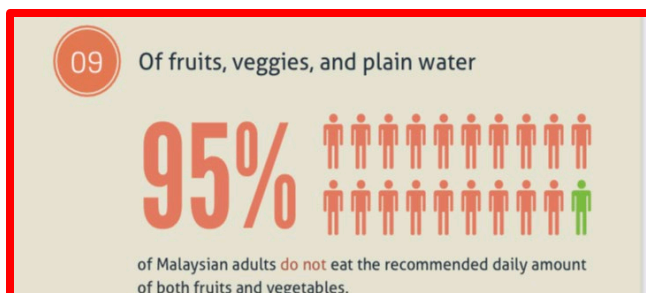
Checking for "People who are at risk" of MAFLD in Malaysian NHMS 2019

Risks for MAFLD

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Diabetics

Being inactive

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1 in 2 adults in Malaysia were **overweight** or **obese**

1 in 2 adults in Malaysia had **abdominal obesity**

04 Diabetes in Malaysia

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Increasing trend

07 Are we active enough?

1 in 4 adults* in Malaysia are **physically NOT active**
* 16 years and above

Checking for "People who are at risk" of MAFLD in Malaysian NHMS 2019
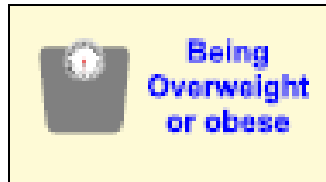
Risks for MAFLD

Being Overweight or obese

Diabetics

Being inactive

Consuming unhealthy diet

We have many MAFLD !

19 Overweight/obesity & abdominal obesity:
A tag team of health risk

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1 in 2 adults in Malaysia had **abdominal obesity**

04 Diabetes in Malaysia

1 in 5 adults in Malaysia have **diabetes**

That's about **3.9 million** people aged 18 years and above

Increasing trend

07 Are we active enough?

1 in 4 adults* in Malaysia are **physically NOT active**
* 16 years and above

09 Of fruits, veggies, and plain water

95% of Malaysian adults *do not* eat the recommended daily amount of both fruits and vegetables.

10 Malaysians and sugary drinks: a not-so-sweet picture

Sugary drinks intake among Malaysian adults

self-prepared drinks — 53.2% daily

carbonated and non-carbonated drinks — 4.2% daily

premixed drinks — 6.7% daily

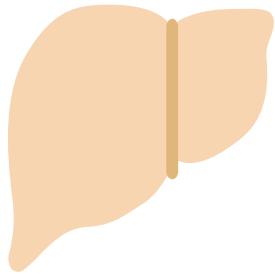M Eslam et al. Hepatology International 2020, NHMS 2019 Institute for Public Health, Malaysia

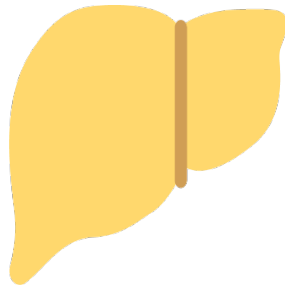# MAFLD represents a spectrum of liver disease severity

Normal Liver

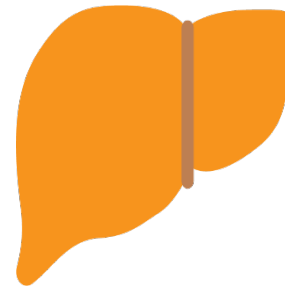**Begins with accumulations of triacyglycerols**

> 5% fatty infiltrations

Steatosis

25% progress from simple steatosis to steatohepatitis

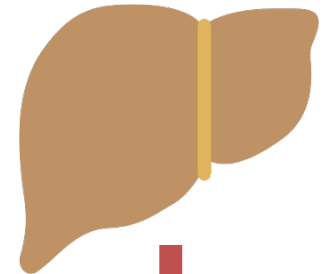**60% can reverse by lifestyle intervention**

Steatohepatitis

NASH reversal is uncommon without intervention

Liver injury -> cell death -> fibrosis

Fibrosis progression 1 stage in 7 years

Cirrhosis

HCC at 1-4% per year

Fan JG et al J Hepatology. 2017. E Jennison et al. Postgrad Med J BMJ 2019

In NAFLD: liver fibrosis, but no other histologic features, associates with long-term outcomes

N=619 NAFLD with liver biopsies (US, Europe, and Thailand)
Follow-up 12.6 years (range 0.3–35.1). 193 (33.2%) died or underwent LT

Survival free of liver transplantation
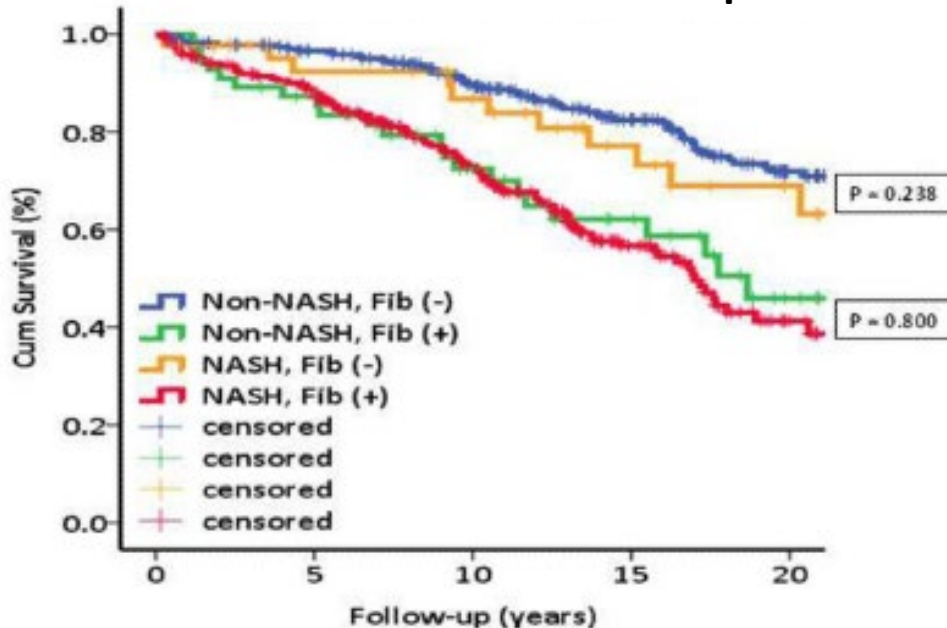
Outcome liver-related events

|	Hazard Ratio	95% CI of HR	P value
Model 1			
Fibrosis, stage 0	1 (reference)		
Fibrosis, stage 1	2.31	0.62, 8.66	0.213
Fibrosis, stage 2	6.68	2.02, 22.06	0.002
Fibrosis, stage 3	13.42	4.24, 42.55	<0.001
Fibrosis, stage 4	52.89	13.31, 210.15	<0.001

Association btn fibrosis stage and outcomes in NAFLD: systemic review & meta-analysis

13 studies : 4428 NAFLD with liver biopsies, 2875 have NASH

All cause mortality   **Liver related events**
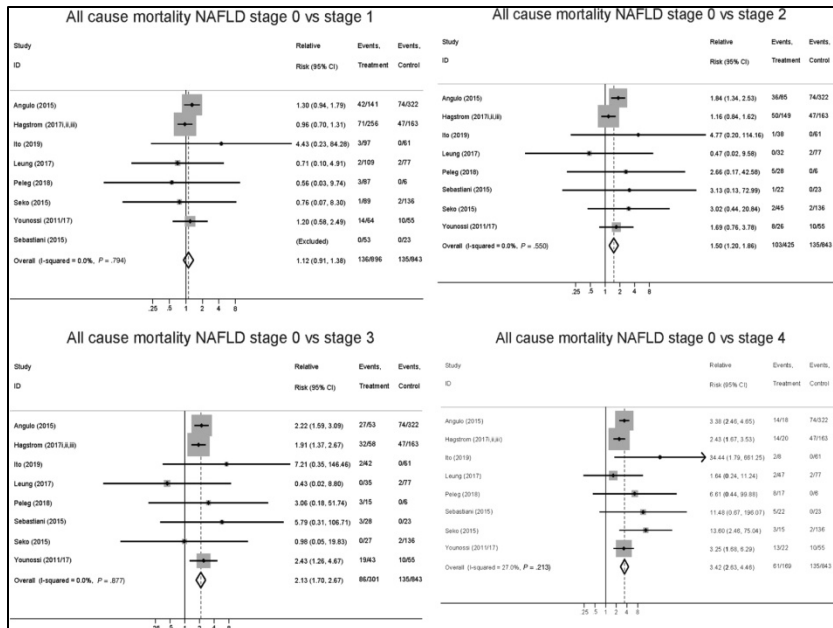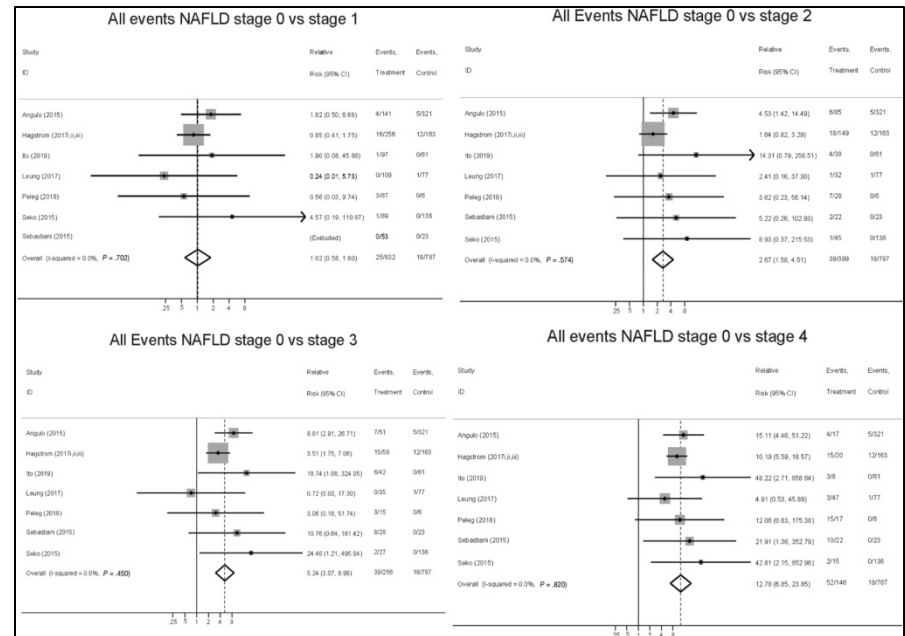
Fibrosis is a key prognostic marker of mortality and liver-related morbidity
Increasing fibrosis stage = 5 to 12-fold increase in RR of liver-related events
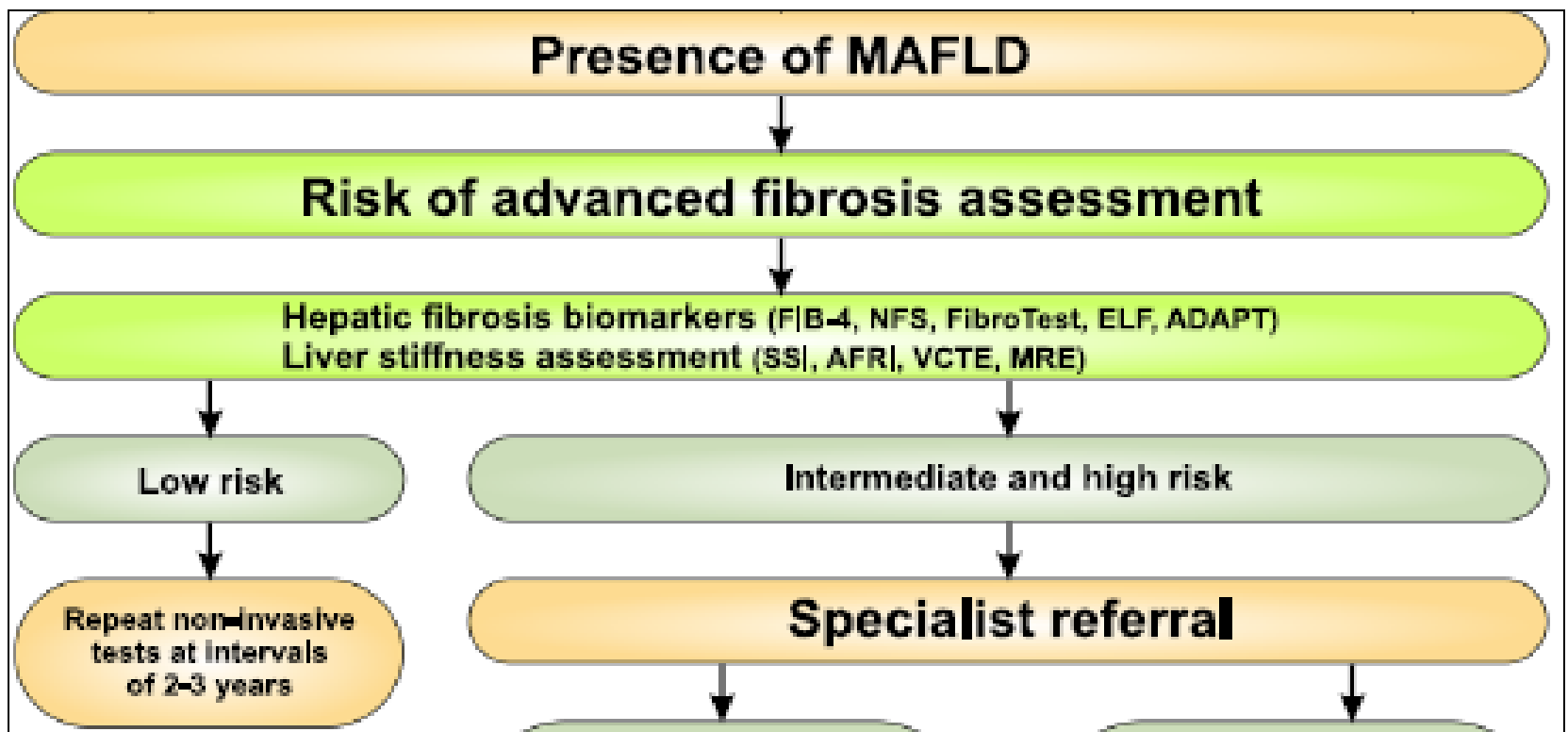
How do I stratify all my MAFLD patients??

WHO NEEDS FURTHER ATTENTION?

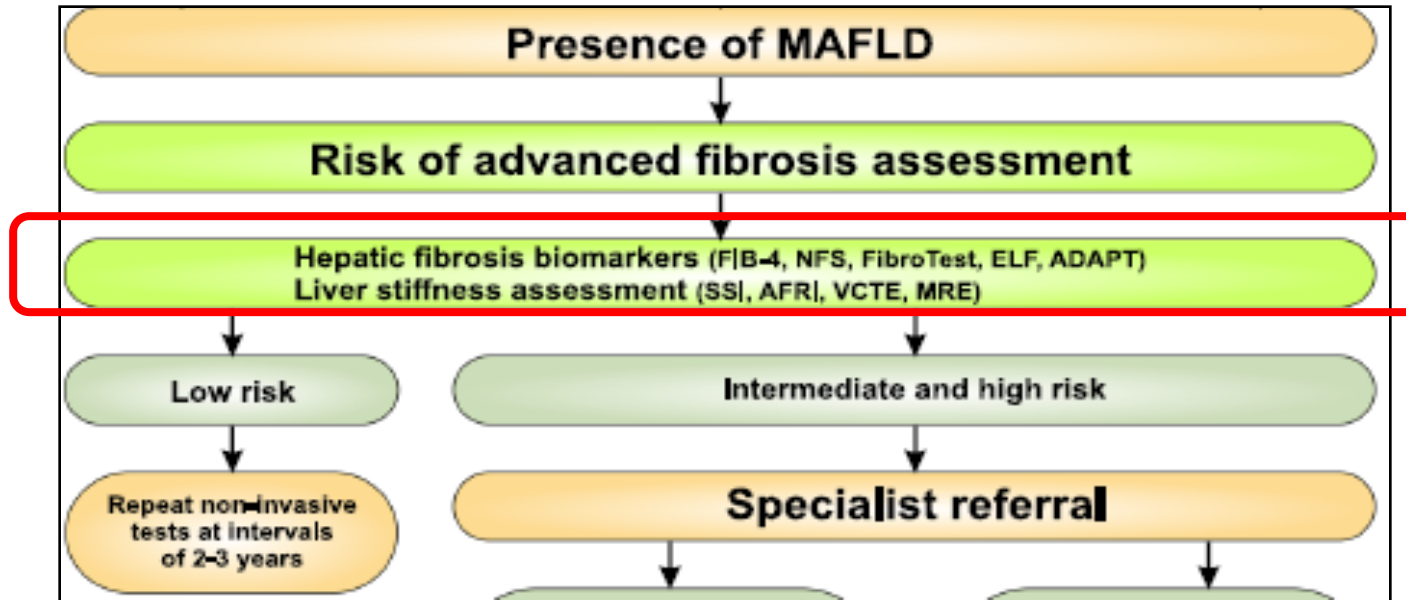**Assessment of liver disease severity and indications for referral**

The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease

Mohammed Eslam[1] · Shiv K. Sarin[2] · Vincent Wai-Sun Wong[3] · Jian-Gao Fan[4] · Takumi Kawaguchi[5] · Sang Hoon Ahn[6] · Ming-Hua Zheng[7,8] · Gamal Shiha[9,10] · Yusuf Yilmaz[11,12] · Rino Gani[13] · Shahinul Alam[14] · Yock Young Dan[15] · Jia-Horng Kao[16,17,18,19] · Saeed Hamid[20] · Ian Homer Cua[21] · Wah-Kheong Chan[22] · Diana Payawal[23] · Soek-Siam Tan[24] · Tawesak Tanwandee[25] · Leon A. Adams[26] · Manoj Kumar[2] · Masao Omata[27,28] · Jacob George[1]

Presence of MAFLD → Risk of advanced fibrosis assessment → Hepatic fibrosis biomarkers (FIB-4, NFS, FibroTest, ELF, ADAPT) / Liver stiffness assessment (SSI, AFRI, VCTE, MRE) → Low risk → Repeat non-invasive tests at intervals of 2–3 years; Intermediate and high risk → Specialist referral

M Eslam et al. APASL CPG Hepato Int 2020

Non invasive tests for liver fibrosis
Blood (simple or specific) and imaging

Presence of MAFLD

Risk of advanced fibrosis assessment

Hepatic fibrosis biomarkers (FIB-4, NFS, FibroTest, ELF, ADAPT)
Liver stiffness assessment (SSI, AFRI, VCTE, MRE)

Low risk

Intermediate and high risk

Repeat non-invasive tests at intervals of 2-3 years
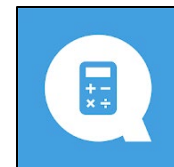
Specialist referral

QxMD

Simple fibrosis scores

FIB-4 {Age, AST, ALT, platelet count}

NFS {Age, AST, ALT, platelet count, albumin, BMI, IFG/DM, }
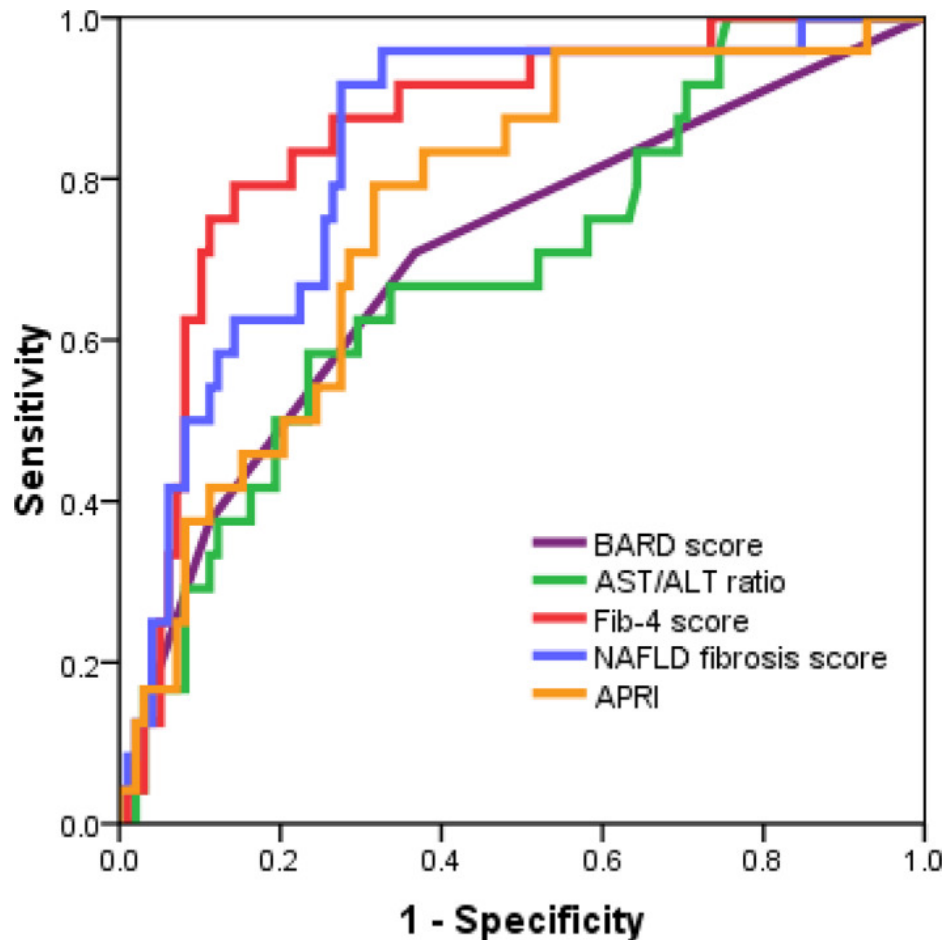
Low, intermediate, or high risk for advanced fibrosis cut-offs :

FIB-4 = 1.30 and 2.67

NFS = < − 1.455 and > 0.676

Use of simple scoring systems for a public health approach in the management of NAFLD

N=122 adult NAFLD with biopsies , 97 (80%) had NASH from UMMC

AUROC :
FIB-4 score (0.86)
NFS (0.84)
APRI (0.76),
BARD score (0.70)
 AST/ALT ratio (0.69)

Use of simple scoring systems for a public health approach in the management of NAFLD

N=122 adult NAFLD with biopsies , 97 (80%) had NASH from UMMC

Table 2 Comparison of the performance of noninvasive scores for the diagnosis of advanced fibrosis in NAFLD patients

Advanced fibrosis

Test	AUROC (95% CI)	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
AST/ALT ratio	0.687 (0.57–0.80)	0.8	37.5	83.7	36.0	84.5
		1	16.7	91.8	33.3	81.8
APRI	0.759 (0.66–0.86)	0.5	83.3	59.2	33.3	93.5
		1	37.5	91.8	52.9	85.7
BARD score	0.702 (0.58–0.82)	2	70.8	63.3	32.1	89.9
FIB-4 score	0.857 (0.78–0.94)	1.3	79.2	84.7	55.9	94.3
		3.25	4.2	98.0	33.3	80.7
NFS	0.836 (0.75–0.92)	−1.455	62.5	77.6	40.5	89.4
		0.676	4.2	99.0	50.0	80.8

FIB-4 and APRI have highest NPV

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FIB-4 and APRI have highest NPV

Table 3 Number of patients avoiding liver biopsy

Test	Cut-off	Patients avoiding referral	False negative result
AST/ALT ratio	0.8	99/122 (81%)	15 (15%)
APRI	0.5	62/122 (51%)	4 (6%)
BARD score	2	69/122 (57%)	7 (10%)
FIB-4 score	1.3	88/122 (72%)	5 (6%)
NFS	−1.455	85/122 (70%)	9 (11%)

Non invasive tests to detect advanced fibrosis in NAFLD

TABLE 2. DIAGNOSTIC THRESHOLDS, AUROC VALUES, SENSITIVITIES, SPECIFICITIES, PPV, AND NPV OF TESTING MODALITIES FOR DETECTING AF IN NAFLD
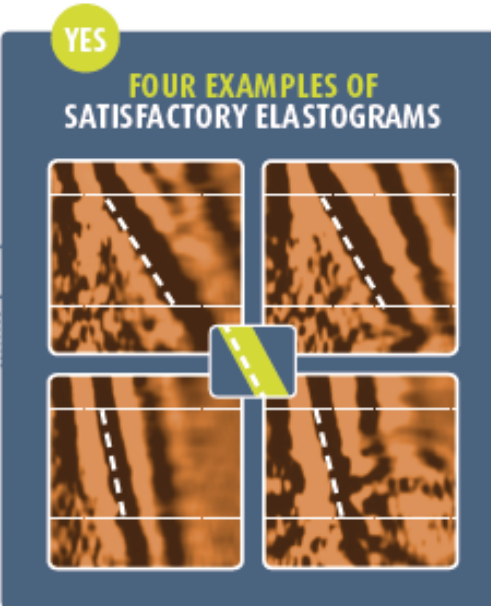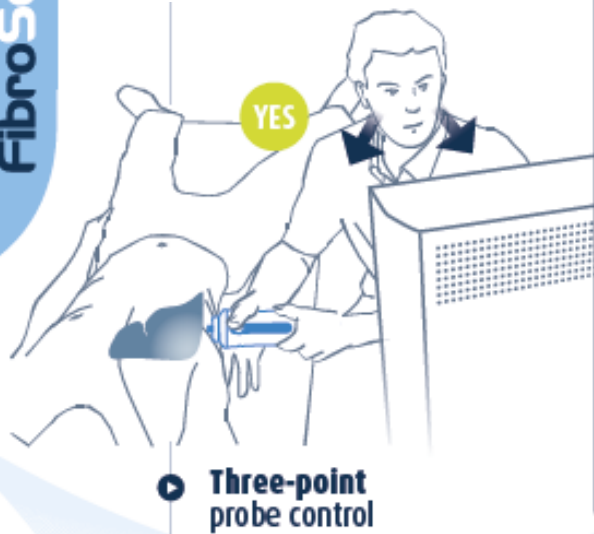
Tests	Cutoffs for AF	AUROC, Mean (95% CI, if Available)	Sensitivity, Mean % (Range, if Available)	Specificity, Mean % (Range, if Available)	PPV, Mean % (Range, if Available)	NPV, Mean % (Range, if Available)
NFS	0.67-0.67	0.78 (0.75-0.81)	43.1 (8.3-100)	88.4 (25.0-100)	66.9 (26.0-100)	88.5 (78.6-100)
APRI	0.54-0.98	0.75 (0.72-0.77)	68.6 (61.0-76.2)	72.7 (59.4-86)	61.4 (46.9-76.2)	77.6 (59.4-94.0)
FIB-4	1.24-1.45	0.80 (0.77-0.84)	77.8 (63.0-90.0	71.2 (55.5-88.0	40.3 (24.0-50.6	92.7 (88.0-98.0)
BARD	2	0.73 (0.71-0.75)	75.2 (41.7-100)	61.6 (32.5-88.9)	38.3 (15.0-79.8)	88.7 (49.6-100)
ELF	0.3576	0.90 (0.84-0.96)	80	90	71	94
FibroTest (FibroSURE)	0.30	0.81	95.0	71.0	31.0	99.0
VCTE (FibroScan, M Probe)	7.6-8	0.87 (0.83-0.90)	87.0 (65.0-100)	77.2 (65.9-90.2)	43.4 (27.0-52.0)	95.5 (86.0-100)
VCTE (FibroScan, XL Probe)	5.7-9.3	0.80 (0.78-0.94)	75.3 (57.0-91.0)	74.0 (54.0-90.0)	58.7 (45.0-71.0)	88.7 (84.0-93.0)
MRE	3.62-4.8	0.93 (0.90-0.97)	85.7 (74.5-92.2)	98.0 (86.9-93.3)	71.0 (67.9-74.5)	93.4 (81.0-98.1)
2D-3D SWE	3.02-10.6	0.91 (0.82-1.00)	89.9 (88.2-91.5)	91.8 (90.0-94.0)	88.2 (83.3-93.1)	93.4 (92.6-94.2)

FIBROSCAN measures liver elasticity

2-3 hours fasting

YES

Three-point probe control

9th to 11th intercostal space

YES

YES
FOUR EXAMPLES OF SATISFACTORY ELASTOGRAMS

Measurement zone at a distance from edges of liver

NO
YES
NO

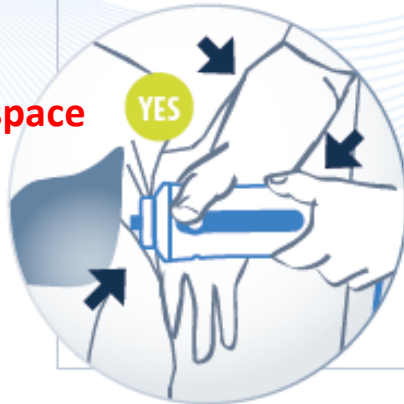**~a cylinder 1 cm wide and 4 cm long, b/n 5 mm and 65 mm below skin surface"**

Controlled Attenuation Parameter (CAP)

Uses US with vibration controlled elastography to measure degree of US attenuation due to hepatic fat. Can detect milder cases
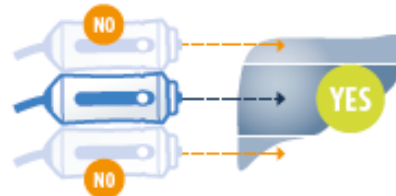
Individual data meta-analysis: CAP optimal cut-offs 248 (237-261) for S0 and 268 (257-284) for S1

(Karlas et al JHep 2016)

Median in kPa, IQR

Adapted from ECHOSEN

Sequential NIT more accurately measured severity of NAFLD than single or simultaneous tests

NIT -> 2 diagnostic thresholds -> a grey zone where dx remained undetermined

Chose the algorithm best suited to the availability of resources locally

Algorithm	Diagnostic accuracy	Sensitivity	Specificity	NPV	PPV
NFS-VCTE	88.5	83.1	92.1	89.2	87.3
FIB4-VCTE	90.7	84.7	94.7	90.4	91.3
FM-VCTE	88.5	83.1	92.1	89.2	87.3
NFS-FMVCTE	85.6	83.1	87.3	88.7	81.1
FIB4-FMVCTE	88.8	86.3	90.5	91.0	85.6
FM-FMVCTE	87.2	84.7	88.9	89.8	83.3
VCTE-FMVCTE	89.8	85.5	92.6	90.7	88.3
FMVCTE	91.1	90.3	91.5	93.5	87.5

J Boursier et al J Hep 2019

Table 3-1: Detailed assessment of a newly diagnosed patient with T2DM

Co-morbidities	• Non-alcoholic fatty liver disease (NAFLD) • Cognitive impairment/dementia • Obstructive sleep apnoea (OSA) • Pancreatitis • Periodontal disease • Low testosterone/hypogonadism in men • Cancers

Non-invasive fibrosis score, such as fibrosis-4 index (refer to Appendix 9), may be used to risk stratify patients with T2DM and NAFLD

(B) Calculating Fibrosis 4 index

$$FIB\text{-}4 = \frac{Age\ (years) \times AST\ (U/L)}{Platelet\ count\ (\times 10^9/L) \times ALT\ (U/L)^{\frac{1}{2}}}$$

FIB-4	Interpretation
<1.3	Low risk for advanced fibrosis
≥1.3	Intermediate to high risk for advanced fibrosis

(A) Use of Fibrosis-4 index in assessment of NAFLD

Elevated ALT and/or AST

US to diagnose fatty liver and exclude focal liver lesion

Exclude other causes of elevated ALT/AST

A liver biopsy may be considered for definitive diagnosis of NASH and/or advanced liver fibrosis in patients with persistently elevated ALT and/or AST, and/or elevated liver stiffness measurement.
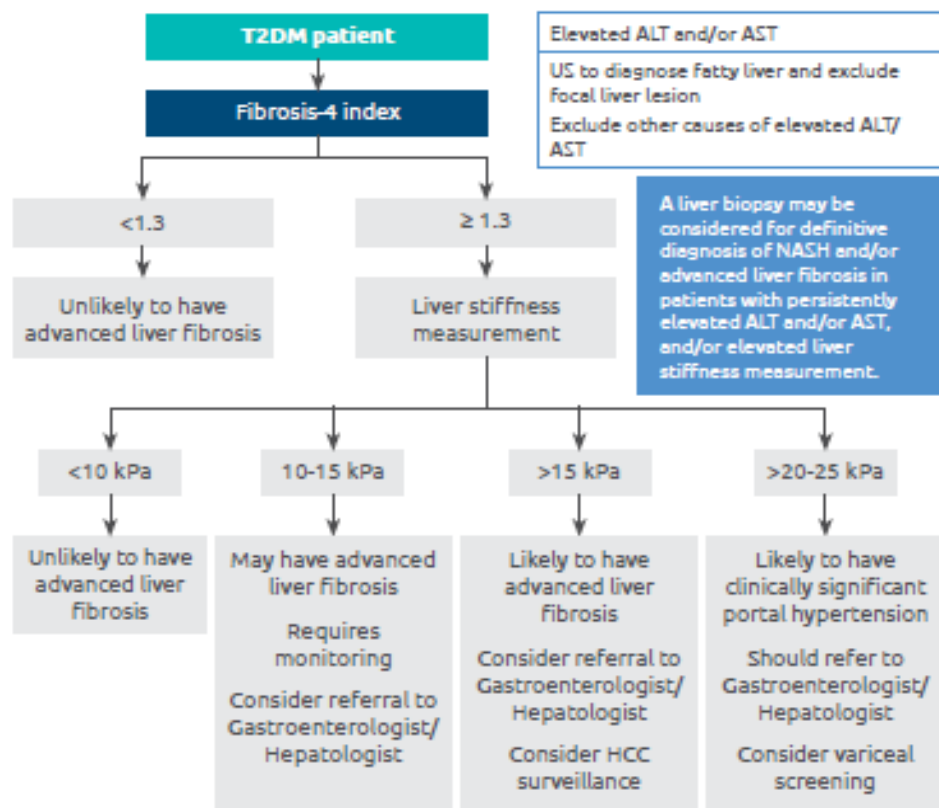
Stratifying liver disease severity also allows appropriate testing, treatment and surveillance
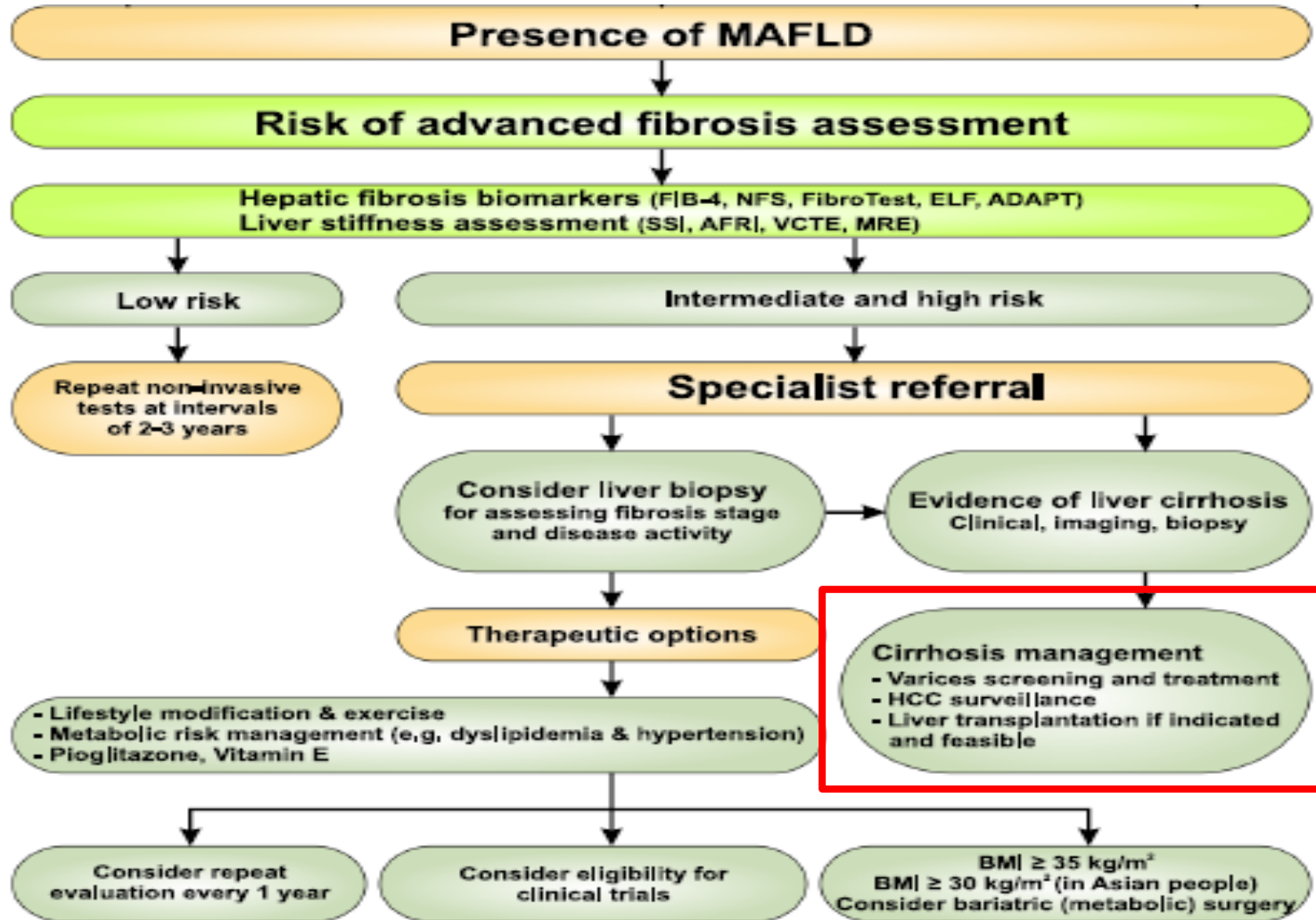
Low, intermediate, or high risk for advanced fibrosis cutoffs:
APRI (0.5 and 1.5), FIB-4 (1.30 and 2.67), NFS (< − 1.455 and > 0.676)

M Eslam et al. APASL CPG Hepato Int 2020

Baveno VI correctly identified 98% who can safely avoid an endoscopy

Compensated disease

Transient elastography & platelets

Liver stiffness <20 kPa AND Platelets >150 → Follow-up

Liver stiffness ≥20 kPa OR Platelets ≤150 → Endoscopy

Decompensated disease → Endoscopy

BAVENO VI: Can we identify low risk cirrhotic patients not requiring endoscopic surveillance for varices?

de Franchis R J Hepatol. 2015;63:743–52; JB Maurice et al. J Hep 2016 65,5 :899-905

HCC surveillance -> early detection increase chance of curative treatment

Level of Evidence	STAGE 0	STAGE A	STAGE B	STAGE C	STAGE D
1	Resection		TACE	Sorafenib (1L) Lenvatinib (1L) Regorafenib (2L) Cabozantinib (2L)	
2	RFA MWA	Resection OLT RFA MWA TARE TACE SBRT	TARE Downsize OLT	Nivolumab (2L)	OLT BSC
3				TARE	

BARCELONA STAGE
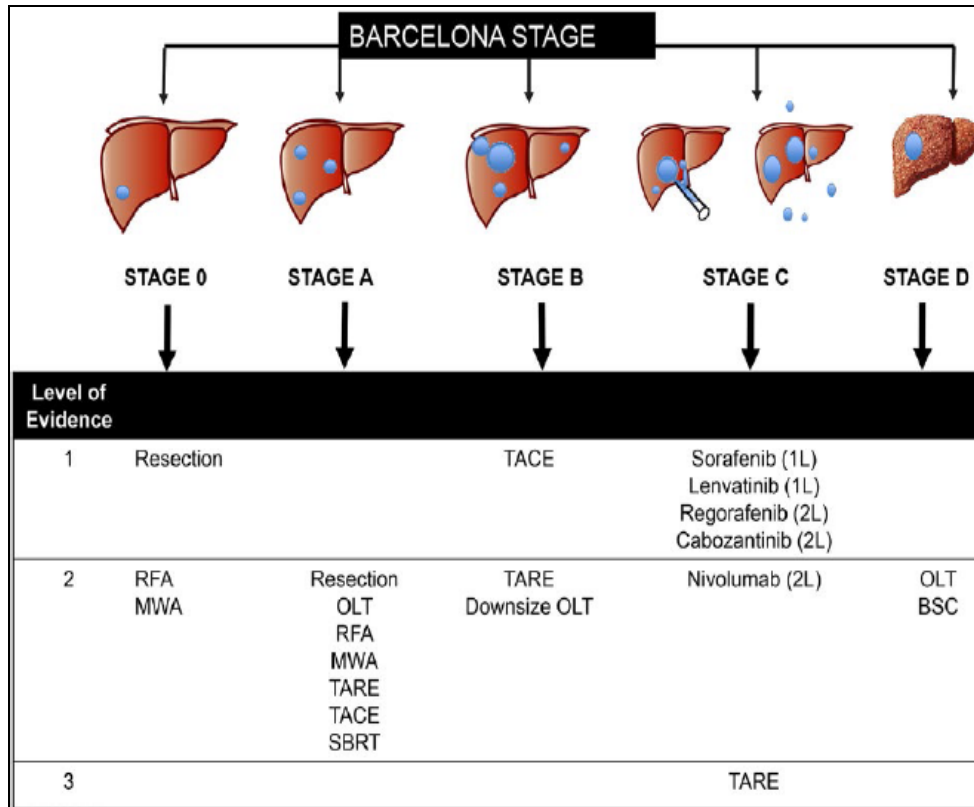
Estimated annual incidence of HCC among NASH cirrhosis : 0.5-2.6%
(surveillance benefit is unclear when incidence of HCC < 1.5%/year)

Marrero et al Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance AASLD, Huang et al Nat Reviews Gastro Hepato 2020
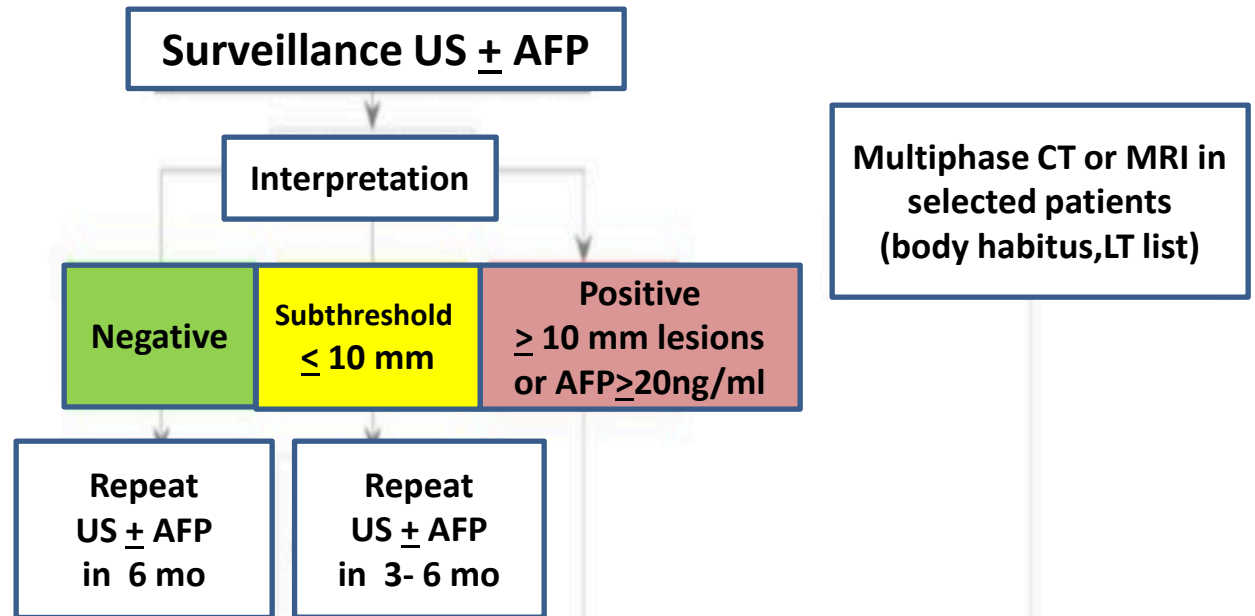
HCC surveillance

SURVEILANCE

Surveillance US ± AFP

Interpretation

Negative	Subthreshold ≤ 10 mm	Positive ≥ 10 mm lesions or AFP≥20ng/ml

Repeat US ± AFP in 6 mo

Repeat US ± AFP in 3- 6 mo

Multiphase CT or MRI in selected patients (body habitus,LT list)

DIAGNOSIS

Diagnostic imaging for HCC multiphase CT or MRI

Interpretation

Marrero et al Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance AASLD
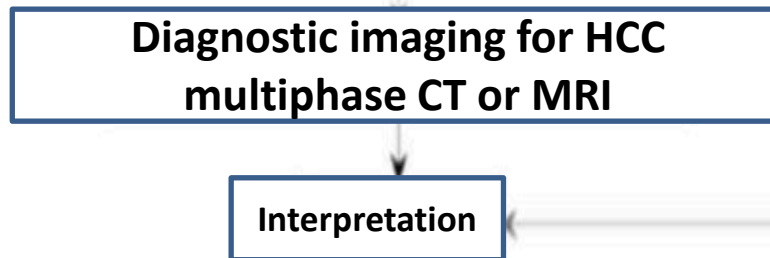
Take to clinic messages

- MAFLD is a common liver disease with a spectrum of severity
- Liver disease progression is dependent on its fibrosis
- FIB-4 is a useful tool to assess for liver fibrosis in primary care setting.
  - FIB-4 < 1.3 -> unlikely to have advanced liver fibrosis
  - FIB-4 $\geq$ 1.3 requires referral for further evaluations

MAFLD
Metabolic Associated Fatty Liver Disease

ALMOST 1 IN 3 OF ADULTS in the APAC region have MAFLD

54 % of global deaths due to **cirrhosis**
73 % of global deaths due to **liver cancer** occurred in the APAC region.

Normal liver ➡ ➡ **MAFLD** ➡ ➡ Steatohepatitis ➡ ➡ Cirrhosis ➡ ➡ Hepatocellular carcinoma

WHAT IS IT?

MAFLD is the build up of extra fat in the liver that is caused by metabolic dysfunction.

If not treated, the liver of about 1 in 5 people with MAFLD can develop scarring.
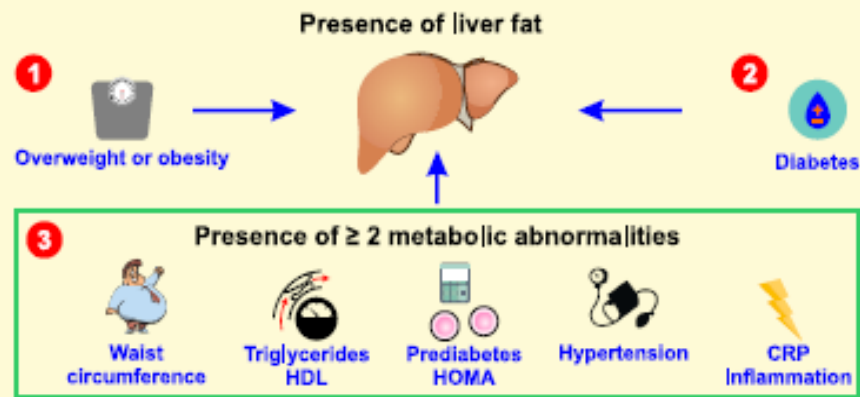
People who are at risk

- Being Overweight or obese
- Diabetics
- Being inactive
- Consuming unhealthy diet
- Between the ages of 40 and 60 years
- Common in both sexes

Symptoms

Typically, there are no symptoms of MAFLD, If they occur, they include:

- Abdominal discomfort
- Tiredness and fatigue
- Nausea

Diagnosis

If you have a risk factor, ask your doctor to check for MAFLD, which can now be easily diagnosed.

Presence of liver fat

1. Overweight or obesity
2. Diabetes

3. **Presence of ≥ 2 metabolic abnormalities**
   - Waist circumference
   - Triglycerides HDL
   - Prediabetes HOMA
   - Hypertension
   - CRP Inflammation

Management

- Diet control
- Lose 7-10% of excess body weight
- Regular exercise
- Avoid smoking and alcohol
- Control diabetes

To learn more about MAFLD visit the APASL website: http://apasl.info/

Mohammed Eslam,… Wah–Kheong Chan..Soek-Siam Tan…. et al , APASL CPG on MAFLD Hepatology International 2020